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Herpesviruses: Silent Instigators of Lung Injury after Hematopoietic Cell Transplant

Although recent advances in the care of allogeneic hematopoietic cell transplantation (allo-HCT) recipients have improved outcomes for this population (1), the overall success of allo-HCT continues to be tempered by noninfectious pulmonary complications. Mortality from idiopathic pneumonia syndrome (IPS) occurring early after transplant remains unacceptably high (2). Bronchiolitis obliterans syndrome (BOS) is a devastating diagnosis associated with diminished quality of life and increased nonrelapse mortality (3). The ability to prevent and treat these conditions has been hampered by a limited understanding of the clinical and biological factors that contribute to their development. In this issue of the *Journal*, Zhou and colleagues (pp. 63–74) build on accumulating epidemiologic evidence of the role of viruses in noninfectious lung disease and provide new insight into the pathogenesis of alloimmune-mediated lung injury after HCT (4).

Reactivation of herpesviruses is common in the first 100 days after allo-HCT and is associated with overall and nonrelapse mortality (5). Using a cohort of over 700 allo-HCT recipients, Zhou and colleagues demonstrate that first infection with human herpesvirus 6 (HHV-6) or Epstein-Barr virus (EBV) is an independent risk factor for IPS, and first post-transplant cytomegalovirus (CMV) infection increases the risk of BOS. The authors applied rigorous statistical methods that considered first viral infection as a time-dependent covariate, adjusted for confounding variables, and accounted for variable follow-up as well as the competing risks for death or disease relapse. Zhou and colleagues then recapitulated these epidemiologic observations in a novel murine model in which mice were infected with an HHV-6 homolog and allowed to develop latent infection before mismatched HCT. Six weeks after HCT, lungs from these preinfected mice demonstrated increased interstitial and peribronchiolar inflammation and BAL fluid TNF-α protein as compared with control mice. These mice also developed skin and gut pathology consistent with acute graft-versus-host disease (GVHD). Notably, the preinfected mice had evidence of viral reactivation by the presence of lung tissue viral polymerase expression but undetectable viral DNA in the BAL fluid (4).

The striking observation here is that reactivation of viruses that are not specific to the lung may be causal for pulmonary injury. Although CMV is a well-recognized cause of pneumonitis in the immunocompromised population, the roles of HHV-6 and EBV are less clear. A provocative study demonstrated detection of HHV-6 DNA in BAL fluid from 20% of patients who were previously diagnosed with IPS (6), suggesting a possible role of HHV-6 in mediating this condition or as an unrecognized cause of pneumonitis. Zhou and colleagues now provide compelling evidence that HHV-6 reactivation is not merely a bystander but may directly contribute to the development of acute lung injury after allo-HCT. In the current study, first post-transplant infections with herpesviruses were also associated with acute GVHD, and a recent meta-analysis further supports this link (7). Taken together, these findings challenge the paradigm of IPS, which is considered noninfectious by definition, and suggest that acute lung injury occurring early after allo-HCT can be a manifestation of an alloimmune response triggered by latent herpesvirus reactivation. Interestingly, first-onset viral infection with CMV was associated with BOS. Although this observation may be surprising given the significant time lapse between infection and disease manifestation, it is consistent with findings in lung transplant recipients, in whom BOS is a more frequent complication (8).

The hypothesis that arises from these findings is that viral infections alter the host immunologic profile in a way that precipitates a proinflammatory and subsequent profibrotic milieu that contributes to acute and chronic organ injury. Furthermore, these results suggest that the immunological sequelae of viral reactivation develop even

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when viral levels are below the threshold of clinical detection. In a broader context, these observations are consistent with a growing body of literature highlighting the role of innate immune activation in regulating the alloresponse to transplantation. Such innate activation may be of particular importance in the context of GVHD given key manifestations in organs at the interface with the external environment, where highly specialized innate defense mechanisms, including the skin, gut, and lungs, predominate. For example, local innate immune activation by the viral pathogen–associated molecular pattern polyinosinic:polycytidylic acid potentiated pulmonary GVHD pathology in a murine model of allo-HCT (9). Moreover, *in vitro* studies demonstrated that polyinosinic:polycytidylic acid exposure enhanced allo-specific lymphocyte proliferation.

Although the work by Zhou and colleagues represents a major step forward, significant gaps remain, and these findings do not yet allow for clinical recommendations regarding HHV-6 or EBV viremia in allo-HCT recipients. Because this retrospective analysis relied on clinically driven viral testing, presumably for a variety of indications, the associations with first herpesviral infections need to be confirmed in prospective studies with standardized viral screening and predefined clinical endpoints. To clarify the contribution of virus to immune activation versus direct lung injury, testing of the lung compartment will be critical, as the immunologic programs that are active in the lung are frequently distinct from those that are active in the blood of patients with acute pulmonary disease (10). Innovative approaches will be required to assess viral activation and immunologic sequelae in the lung, including host gene expression profiling, an emerging tool for pathogen-associated disease assessment, which could be applied to paired blood and BAL samples (11). The impact of first infection with community-acquired respiratory viruses, which have been implicated in the development of BOS (12), was also not fully addressed due to the low number of confirmed events, a limitation acknowledged by the authors. That early CMV infection can set the stage for chronic lung injury in an allograft setting is a plausible hypothesis bolstered by this study, but the cumulative infectious and noninfectious triggers that lead to BOS months after the initial insult remain undefined.

Ultimately, the findings of Zhou and colleagues add to a call to arms, emphasizing a critical need to move beyond retrospective and preclinical studies into prospective, multicenter investigations. Such a collaborative initiative, in which investigators could follow allo-HCT recipients longitudinally from the time of transplantation to collect the appropriate biospecimens and correlative clinical data, would provide a well-phenotyped cohort to support appropriately powered clinical risk factor analyses and translational studies. The time to move forward collectively on post-HCT lung disease has never been more opportune. Not only do we have innovative tools to understand the biology of occult viral infections and innate–alloimmune interactions, plausible treatments are also emerging, including novel antiviral agents in active development (13, 14). If the lung pathology associated with herpesvirus reactivation is confirmed, determining whether we can prevent or treat it, and in whom, will require randomized, controlled, interventional studies. As current approaches have been shown time and again to fail patients with IPS and BOS, unraveling the pathways to lung injury after allo-HCT is an urgent necessity to improve clinical outcomes for these patients. ■

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Body Composition in Childhood: Is the Window for Influencing Lung Function Still Open?

The impact of early-life factors on adult lung disease has been increasingly recognized since the pivotal work by Barker and colleagues in the 1990s (1). Early-life developmental factors have been systematically studied, and birth weight has been shown to be a consistent factor in determining the maximal lung function achieved (2). Catch-up growth and early growth also have shown small but significant influence on adult lung function (3). Childhood respiratory factors have been studied in longitudinal cohorts to hone and predict adult lung function and risk profile for adult chronic obstructive pulmonary disease (COPD) (4, 5). At least half of all cases of COPD can be attributed to childhood factors and not achieving peak lung function in early adulthood (6, 7).

The changing demographic of the growth pattern in children and adolescents has shown increasing obesity across the world (8). There is evidence to suggest that weight gain in late childhood is associated with reduced lung function (3), and a meta-analysis has shown obesity to be detrimental to lung function (9). In longitudinal studies where asthma was followed prospectively, the lung function trajectory appears to be set early in life and continues to track into adulthood (10).

Although there is unequivocal evidence that pediatric and developmental factors determine adult lung function and thereby influence adult morbidity, it is important that we look for signals in our birth and longitudinal cohorts to tease out factors and patterns that might be amenable to modification or intervention.

In this issue of the *Journal*, Peralta and colleagues (pp. 75–83), have examined growth patterns through childhood, specifically body composition trajectory, and studied the relationship to lung function at 15 years (11). Their premise was that the commonly used body mass index (BMI), which related height and weight, was not sensitive enough to examine relationships between growth and lung function. They used the data from the ALSPAC (Avon Longitudinal Study of Parents and Children) to determine the influence of body composition trends, collected through 9 to 15 years of age, on lung function measured at 8 and 15 years of age.

The unique feature of this study was looking at body composition in terms of lean BMI (LBMI) and fat mass index (FMI) and tracking each of these variables through childhood. A novel statistical tool has been used to derive the trajectories, and clear patterns and trends are observed across the ages in both LBMI and FMI (12). The impact on lung function shows significant differences between LBMI and FMI trajectory groups. Very clearly, in both sexes, a greater increase in LBMI confers higher lung function growth. This is present for all lung function values FVC, FEV_1, and forced expiratory flow, midexpiratory phase ($FEF_{25–75}$). In boys, it was 0.62 L increase in FVC in the highest trajectory group compared with the lowest trajectory, 0.53 L increase for FEV_1, and 0.53 L/s increase for $FEF_{25–75}$. In girls, it was 0.37 L increase for FVC, 0.30 L increase for FEV_1, and 0.35 L/s increase for $FEF_{25–75}$. The association is strong and persisting, even after correcting for a range of variables that have been shown to impact lung function. On the other hand, the FMI shows variable associations with significant negative association for FEV_1 (−0.14 L), $FEF_{25–75}$ (−0.20 L/s), and FEV_1/FVC (−1.44) in boys and FEV_1/FVC (−2.05) only for girls between the lowest trajectory group to the highest trajectory group.

This study gives us insight into inconsistencies that have been reported in the association between BMI and lung function in other longitudinal studies. An increase in both lean body mass and fat mass will increase BMI, yet the data reported by Peralta and colleagues show the very different influences that these have on lung function growth (11).

The method used by Peralta and colleagues for deriving trajectories is a useful addition in interpreting complex longitudinal datasets, and, as the authors rightly point out, there is potential risk for smoothening effect (11). In experienced statistical hands, these tools will help us in understanding growth trends and their effects.

In addition, they have also looked at the rate of growth of lung function from 8 to 15 years of age, and the linear association with LBMI is seen strongly across all lung function values. Looking further ahead, it would be reasonable to hypothesize and investigate further whether higher LBMI trends in childhood and adolescence lead to slower decline in lung function through adulthood.

Lung function trajectories appear to be set early (13), and this study raises the question of the appropriate window to intervene in terms of body composition to influence eventual peak lung function achieved.

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